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Physical and Chemical Bases for the Use of Artemisinin as a Sonosensitizer for SDT Treatments

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ABSTRACT

Artemisinin ($ARTO_2$) has been used as a successful drug to control malaria and has also been proposed as an anti-cancer drug. Many authors have argued in favor of that last use. The combined use of $ARTO_2$ with ultrasound (US) was developed earlier and it has also been reported a complex mechanism of action which needs the simultaneous presence of $ARTO_2$, iron and US. Over simplifying we can affirm that the $ARTO_2$ peroxide moiety reacts with iron as in Fenton's processes to form cytotoxic free radical. On the other hand, US irradiation can create hydrodynamic stress (sonomechanical process), inertial cavitation (pyrolitic process) and long range effects mediated by radicals or ROS. Sonochemical reactions can be originated by pyrolytic like process, shock mechanical waves, thermal reactions and radical and ROS mediated reactions. Sonolysis of pure water can yield hydrogen or hydroxyl radicals and hydrogen peroxide (ROS) but non ROS production was observed in 1,4 dioxane as a solvent. The effect of US on peroxidic compounds was not adequately studied, and then we have explored the behavior of some natural and synthetic compounds. When ARTO2 in 1,4 dioxane solution is irradiated with 20 or 24 kHz and different power intensity the production of molecular singlet oxygen is observed. Specific scavengers like Tetracyclone (TC) are used to demonstrate it. We define sonosensitized reaction as one in which a chemical species decompose as consequence of cavitation phenomena producing ROS or other radicals and some other target species does undergo a chemical reaction. The concept was gotten from previous work and extended to other peroxides like ARTO2. We show that artemisinin is an endoperoxide and behaves as a sonosensitizer in the sense of our definition.

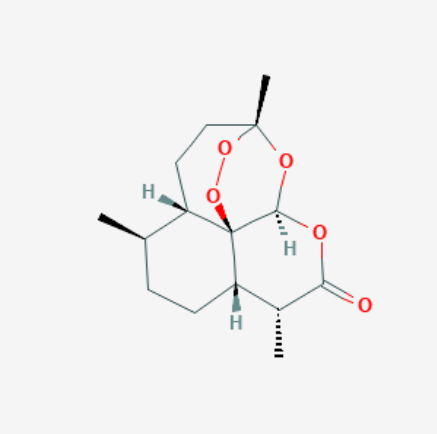
3. Introduction

3.1. Artemisinin and their Physiological Effects

Tu Youyou wins the Nobel Prize for Medicine in 2015 for the discovery of a novel therapy against malaria. She combined ancient knowledge contained in a more than 2000 years old text and her own experience about the cold extraction from Artemisia annua herb [1]. Artemisinin ($ARTO_2$) is today the most famous molecule used against malaria. Its use helps to save millions of lives each year. $ARTO_2$

From Chemical point of view artemisinin as a modern drug, is a sesquiterpene lactone containing an unusual peroxide bridge. This endoperoxide 1,2,4-trioxane ring is responsible for the drug's mechanism of action. As it was depicted elsewhere [2] the antimalarial activity is related mainly but no uniquely to the combined action of iron

(Fe II) and peroxide artemisinin molecule moiety and like in Fenton reaction, ROS (reactive oxygen species, specifically HO·) are produced.



$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO\cdot + HO^-$

Since more 20 years it is accumulated an important evidence of the anticancer effect of artemisinin and their derivatives. Activity against cancer cells in vitro, in vivo and many modes of action with multiple targets were proposed [3]. In parallel many clinical studies were performed too. Today it is accepted that the general use of artemisinin and their synthetic derivatives as anticancer drug need more clinical and pharmacokinetic studies in order to answer questions related to tolerability, mode of administration, side effects, and dose between others.

3.2. Ultrasound, Matter and SDT

Photodynamic Therapy (PDT) is based on photosensitized production of highly reactive oxygen species (ROS) by irradiation of a Photosensitizer (PS). Photosensitized reaction is defined as one in which a chemical species (PS) having absorbed light shows no overall chemical change, but as a consequence some other species does undergo a chemical reaction (electron transfer, energy transfer process , etc). Even when the precise mechanism of PDT is not yet fully understood it is accepted that the main ROS species is the singlet molecular oxygen as the main toxic product. In spite of the advances in the photodynamic treatment of cancer, not always is possible to illuminate adequately the tissues affected, and being this point an important obstacle in the effective application of this therapy. Sonodynamic therapy (SDT) has been developed as a novel non-invasive approach. An earlier work of Yumita et al. [4] demonstrates that some photosensitizators can produce important cell damage when they were activated by ultrasound instead light. How the sound can activate the photosensitizers?.

3.2.1. Ultrasound and chemistry: The ultrasound is utilized with relative success in the degradation of billiards stones, as stitch up and in such experimental advanced surgical techniques (eg: HIFU, High-Intensity Focused Ultrasound). The chemical effects of the ultrasound, do not originate as opposed to that occurs in photochemistry by the direct coupling of the acoustic field with energy levels of molecules. The most important not lineal acoustic process of the sonochemistry is the cavitation that leads an enormous concentration and conversion of the mechanical energy. As it was depicted elsewhere the inertial cavitation involves three phases: i) nucleation, ii) growth of the bubbles and finally under appropriate conditions, iii) its implosion. The nucleation corresponds to the formation of cavities in a liquid bulk and is a process that depends on its tensile force. The cavities will be generated for effect of the negative pressure of an acoustics expansion wave only in certain points of the liquid that feel some type of "failure". Finally some bubbles of a given size during the positive cycle of compression acoustics can culminate implossing. At the imploding cavities the local temperature and the local pressure have been said so high like 5000°C and 500 atm. respectively [5]. Sonochemical reactions can occur in three different regions: the first one is the interior of the collapsing bubbles where the pyrolytic like reactions take place. The second region is the turbulent interface between the bubbles and the bulk solvent where thermal decomposition can take place. The third region, the bulk solvent, can be reached by the free radical and such other active species with large lifetime to produce similar reactions to those produced in dark photochemistry or in radiation chemistry.

3.3. The Sonosensitizator Concept

Because the high energy involved during cavitation process ultrasound itself can be used to destroy cells in a massive way like in HIFU [6]. Another strategy which could be less aggressive is to use sonosensitizators. Then, sonodynamic therapy could be an analogous approach based on the synergistic effect of ultrasound and chemical compound referred to a "sonosensitizer". Thus, water-soluble azo compounds have been considered as sonosensitizers. These are

a thermally labile molecule which decompose by pyrolysis in the cavitation bubbles or decomposes near them to form molecular nitrogen and radicals [7]. These molecules in the presence of oxygen form peroxy radicals which are cytotoxic.

On the other hand some sonochemical process mediated by molecular singlet oxygen has been frequently suggested for hematoporphyrin derivatives, photofrin, adriamycin, rose Bengal, piroxicam and others [8,9]. Several studies have investigated the mechanisms by which ultrasound promotes apoptosis in various cancer cell lines in the presence of "sonosensitizers". It has been proposed that this effect is originated from the cavitation phenomenon.

As it was said before, according Tachibana [10], cavitation can be classified into stable (oscillating bubbles) and inertial (collapsing bubbles). Both kind of process are capable to generate mechanical effects on the membranes. Thus, in conditions of stable cavitation rapid flow of liquid is produced around the bubbles, which can induce shear stresses to membranes. In inertial cavitation the violent collapse of the bubbles produces a shock wave and fluid jets, which have been shown to cause dramatic changes in the cell membrane morphology [11]. Also, it has been proposed that the inertial cavitation can cause an increase in the permeability of membranes (sonoporation) and it was recognized that only inertial cavitation can induce sonochemical reactions due to ROS generation [12].

The increased permeability of membranes could, in some way, explain the increased mortality of cells in the presence of cytotoxic agents when are treated with ultrasound.

It was recognized that a disadvantage of some sensitizers, is the relatively poor tumour affinity and long clearance time which can lead to toxicity in normal tissues. In this sense X. Pang and others [13] describe a review of the effect of sonosensitizers derivated from natural products. These compounds are such as porphyrins from blood, chlorophyll derivatives from green plants and silkworm excrement, hypocrellins from Hypocrella bambuase and curcumins from Curcuma longa. They have the advantage of being eliminated rapidly from the organism.

There is no conclusive evidence so far that cavitation can also occur intracellularly, but such an event would lead to immediate cell destruction because the resonant size of the cavitation bubble till the low MHz range is comparable to the size o cells [14]. To avoid this difficulty, Nanobubbles (NBs) can be used instead large bubbles (micro bubbles, MBs). As it was sated [15], despite the broad studies on NBs, the mechanisms of the whole principles including nucleation, formation, and stability of NBs are not well known yet. In order to induce the decrease of size of MBs to the nanoscale, pluronic acid, an amhiphilic surfactant, was reported to have this ability [16] which is reflected on the number of papers on NBs which is increasing fast. Some authors said that because the widely structurally different compounds which have been reported to have sonodynamic activity it is difficult to expect a universal mechanism for the synergism between ultrasound and drugs. Even when it is probably true we need to propose a more precise definition of sonosensitizer.

The primary effects of US (ultra sound) like mechanical stress mentioned above, global and local heating will not consider into the sonosensitizer concept. Those phenomena are normal effects related to the sound and matter interaction.

We have proposed a general sonosensitizator definition [17], which can be depicted as follow:

$$S \xrightarrow{US} P + ROS$$

$$ROS + Q \longrightarrow product$$

Where S is the sonosensitizer, P is a stable compound and Q is a target could be Tetracyclone (TC) or a biological compound. TC is a well known specific singlet oxygen scavenger.

We define sonosensitized reaction as one in which a chemical species decompose as consequence of cavitations phenomena producing ROS or other radicals and some other target species does undergo a chemical reaction. We try to extend the concept to the peroxides family, endoperoxides, quinones, and others.

We can also take into account the specifically chemical effects of US on the solvent. For example when a sonic horn irradiates in pure water and inertial cavitations takes place then the following reactions were depicted by many authors [5]:

$$H_2O \longrightarrow H\cdot + \cdot OH$$

$$HO\cdot + \cdot OH \longrightarrow H_2O_2$$

$$H\cdot + \cdot H \longrightarrow H_2$$

The first reaction corresponds to the pyrolysis of water in the implosive core of bubbles; the others are radical recombination

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to yields hydrogen and hydrogen peroxide, an aggressive long lived oxidant.

4. The "Peroxide project"

We have demonstrated that DPAO2 (9,10 Diphenyl anthracene endoperoxide) can generate singlet molecular oxygen with high efficiency [17] when it is sonolized.

We find that is possible to split natural and synthetic endoperoxides mediated mechanical waves (ultrasound) to generate ROS and then it becomes in good sonosesitizer.

By an adequate focused mechanical wave arrays would be able in principle to treat almost any zone of an alive organism that contains the active principle (sonosensitizer).

We have studied the behavior of different peroxides: Anthracene derivatives, ascharidol, triperoxy ketone and diperoxy ketone and artemisinin between others with good result. (Not published results). In the same way than for $DPAO_2$, we demonstrate that artemisinin ($ARTO_2$) is like a singlet oxygen store molecule.

5. Sonolisis of $ARTO_2$ in Absence of Iron: Results and Discussion

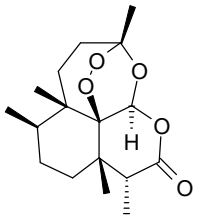
Now we can back to an important question: How the sound can activate the photosensitizers?. The light that came from sonoluminiscence was observed as responsible of the sonosensitizator excitation (when it is a photosensitizator too) and ulterior ROS production [18]. In the presence of iron, in dark and in "silence" ROS production was explained by Fenton like reaction between iron and $ARTO_2$ peroxide moiety. Some interesting works have been doing recently showing the mechanistic details both in vitro and in vivo [3,18-20]. Thus, ARTO2 has been observed to be tightly linked with characteristic of ferroptosis as a novel iron related cell death process [2].

However, Fenton processes do not exhaust the possibilities of $ARTO_2$ as sonosensitizer. We have demonstrated that for the decomposition of peroxides like $DPAO_2$ and $ARTO_2$ to produce ROS, is not necessary to invoke nor sonoluminescence, neither Fenton process.

Then, even in the absence of iron it is possible to think in ROS generation. The follow lines show how is possible that ARTO2 can works as a sonosensitizer in the sense depicted before.

First at all, ARTO2 is a peroxide compound and all the peroxide compounds that we have studied till now decompose in an acoustic field of the appropriate power to yield ROS.

This mechanism is not proposed to replace Fenton like process if not to sum a new one in order to understand the complex action of $ARTO_2$ combined with US.



$$\xrightarrow{\phi\ /\ \sim} \text{Productos} + {}^1O_2 + {}^3O_2$$

Sonosensitization process: kinetic scheme

$$ARTO_2 \xrightarrow{k^1_s} {}^1O_2 + P \qquad [3.1]$$

$$\searrow^{k^2_{\tau}} \quad {}^3O_2 + P$$

$$O_2(^1\Delta_g) \xrightarrow{k^1} {}^3O_2 + \text{heat} \qquad [3.2]$$

$$O_2(^1\Delta_g) \xrightarrow{k^2_d} {}^3O_2 + h\upsilon \qquad [3.3]$$

Reactive pathways (inhibitors or target molecules)

$$^1O_2 + Q \xrightarrow{k_q} {}^3O_2 + Q \qquad [3.4]$$

$$^1O_2 + Q \xrightarrow{k_r} \text{product} \qquad [3.5]$$

$$^1O_2 + TC \xrightarrow{k_r} \text{product} \qquad [3.6]$$

Where P is an stable compound, ROS is in this case is singlet molecular oxygen, (O2(1Dg) and Q is a target which could be TC (Tetracyclone), or a biological compound.

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The kinetic scheme of the sonolysis of $ARTO_2$ contemplates sensitization equations (3.1), the decay of singlet molecular oxygen in 1,4-dioxan equations (3.2) and (3.3) and reaction between singlet molecular oxygen and tetracyclone, equation (3.6).

Equations derived from the kinetic scheme:

Assuming that Vs is the artemisinin sono decomposition velocity, then:

$$Vs = - \delta [ARTO_2] / \delta t = \delta [^1O_2 + {}^3O_2] / \delta t = (k^1_S + k^2_T) [ARTO_2]$$

$$Vs = (k^1_S + k^2_T) [ARTO_2] \quad \textbf{[3.7]}$$

$$\text{And } Vr = - \delta [TC] / \delta t = - \delta [^1O_2] / \delta t = kr [TC] [^1O_2] \quad \textbf{[3.8]}$$

Where Vr is the velocity of singlet molecular oxygen reaction with TC. The singlet molecular oxygen is that generated by sonodecomposition of $ARTO_2$.

Now making the rate between eq (3.8) and eq (3.7) we get:

$$Vr / Vs = (\delta [^1O_2] / \delta t) / (\delta [^1O_2 + {}^3O_2] / \delta t) = \varphi^1O_2 \quad \textbf{[3.9]}$$

Where $\varphi\ ^1O_2$ is the efficiency of $ARTO_2$ to yield singlet molecular oxygen

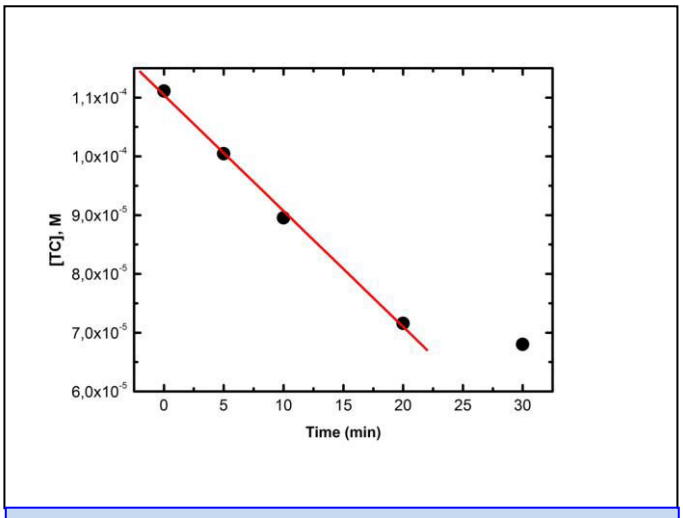

Figure 1: Sonolysis of $ARTO_2$

TC consumption by ROS generated by Artemisinin
(Reactor: 24 kHz, near 15 W, time between 0 and 30 minutes, initial [TC] = 1.1 x 10-4 M.)

The (Figure 1) shows typical experiments which were performed in 1,4 dioxane with different artemisinin concentrations between 1 x 10^{-3} M and 5 x 10^{-5} M. Tetracyclone (TC) was used to test the singlet oxygen generation during sonolysis and as always followed by UV-visible spectroscopy as it was depicted elsewhere [17].

For a DPAO2 as sonosensitizer $\varphi\ ^1O_2$ we found as 0.85. Unfortunately we were not able to measure this parameter for $ARTO_2$. Instead that, we can compare de singlet oxygen stationary concentration for both sonosensitizers at such conditions.

Thus, from the kinetic scheme assuming stationary condition we can get:

$$[^1O_2] = \frac{k^1_S [SONOSENSITIZER]}{k_d + kr [TC]} \quad \textbf{[3.10]}$$

where $kd = k^1_d + k^2_d$

Replacing (3.10) in (3.8) for each sonosensitizor ($DPAO_2$ and $ARTO_2$) to get $Vr_{(DPAO2)}$ and $Vr_{(ARTO2)}$ and making:

$$\frac{Vr_{(ARTO2)}}{Vr_{(DPAO2)}} = \frac{[^1O_2]_{(ARTO2)}}{[^1O_2]_{(DPAO2)}} = \frac{k^1_{S\,(ARTO2)}}{k^1_{S\,(DPAO2)}} \quad \textbf{[3.11]}$$

Thus, that ratio transforms to equation (3.11) which results the quotient between the singlet molecular oxygen stationary concentrations generated by both sonosensitizers measured at the same power irradiation, reactor geometry and TC concentration. Equation (3.11) also represents the ratio between the specific rate constant for the peroxide decomposition to produce singlet molecular oxygen (k^1_S) for both sonosensitizers.

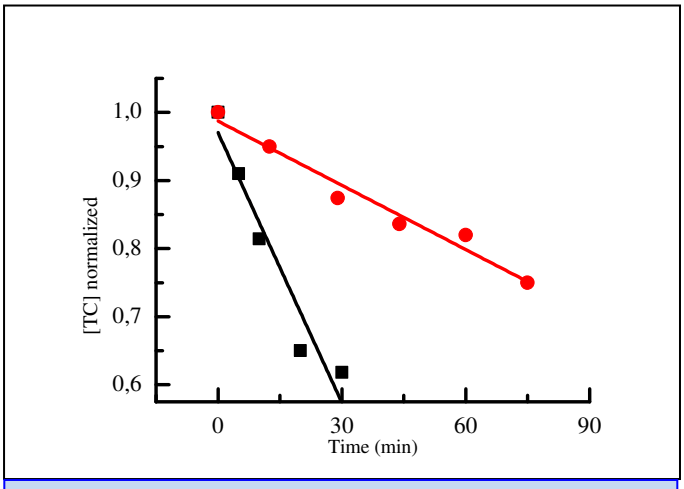

Figure 2: Comparison of $ARTO_2$ and $DPAO_2$ as sonosensitizers.

Normalized [TC] consumption by ROS generated by $ARTO_2$ or by $DPAO_2$.

(Reactor : 24 kHz, near 15 W, time between 0 and 75 minutes, initial [TC] = 1.1 x 10-4 M or 5.0 x 10-4 M for $ARTO_2$ and $DPAO_2$ respectively. [$DPAO_2$]= 3.85 x 10-5 M), [$ARTO_2$] =4.0 x 10-5 M)

(Figure 2) shows the comparative rate of decomposition of $DPAO_2$ and $ARTO_2$. The ratio results:

$$\frac{Vr_{(ARTO2)}}{Vr_{(DPAO2)}} = 1.2$$

in this experiments the TC concentration was five times higher for $DPAO_2$ deomposition than for $ARTO_2$ case then :

$$\frac{Vr_{(ARTO2)}}{Vr_{(DPAO2)}} = 1.2 = \frac{1}{5}\frac{[^1O_2]_{(ARTO2)}}{[^1O_2]_{(DPAO2)}} \quad \text{then,}$$

$$\frac{[^1O_2]_{(ARTO2)}}{[^1O_2]_{(DPAO2)}} = 6$$

The singlet molecular oxygen stationary concentration results six times higher for the case of $ARTO_2$ than for $DPAO_2$ measured at the same conditions. We think that this could establish a way to develop a quantitative comparative efficiency of different sonosensitzers. Of course this is not the only mechanism for $ARTO_2$ action.

6. Material and Methods

Sonolysis experiments were performed in a glass made reactor (cylindrical vessel) , with cooling system for using Sonoprocessor Hielscher UP 200S (24 kHz), with a 14 mm microtip and variable power 0-200 W (and PC controlled). In all cases the temperature was hold near to 15°C. The solvent was 1,4 Dioxane because no ROS are generated during the sonolisys of the solvent alone. Besides the regular experiments we use the following controls: i-sonolysis of the quencher alone (TC), ii-sonolysis of solvent and iii-thermal reaction between sonosensitizer and quencher in the solvent without ultrasound. In all experiments shown in this paper the results of controls were negative.

4. Conclusion

Artemisinin ($ARTO_2$) is an endoperoxide and behaves in the same way that the peroxides we have studied before, that is, it decomposes producing singlet molecular oxygen when it is irradiated with US at the appropriate frequency and power. The inertial cavitation in a stable solvent in the absence of iron lead to ROS production from $ARTO_2$ sono decomposition. The evaluation of its effectiveness was carried out by means of a method that we have developed and that allows to compare the relative reaction rates of molecular singlet oxygen with the scavenger TC. As a reference compound we use $DPAO_2$ whose singlet molecular oxygen generation efficiency was determined as high as 0.85. Although we could not measure the efficiency of $ARTO_2$, we were able to establish the relative stationary singlet molecular oxygen concentration which results six times higher for $ARTO_2$ measured in similar conditions. The increase in the antitumor activity of $ARTO_2$ combined treatment with the US has had the classic explanation which implies the Fenton's reactions. We demonstrate the existence of a new and efficient mechanism for ROS generation from $ARTO_2$ which converts it to an efficient sonosensitizer in the sense of our definition. The experimental evidence is very solid and that is why we think that under conditions of inertial cavitation it could be the predominant mechanism in solution. In order to conclude this definitively, experiments should be performed *invivo* to try to elucidate the relative importance of the proposed new mechanism related to the role of collapsing bubbles (MBs and NBs).

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